Institute Report No. 406

Primary Dermal Irritation Potential of DIGL-RP Solid Propellant in Rabbits

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and
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MAMMALIAN TOXICOLOGY BRANCH
DIVISION OF TOXICOLOGY

October 1989

Toxicology Series: 160

LETTERMAN ARMY INSTITUTE OF RESEARCH
PRESIDIO OF SAN FRANCISCO, CALIFORNIA 94129

Primary Dermal Irritation Potential of DIGL-RP Solid Propellant in Rabbits (Toxicology Series 160)--Brown and Korte

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This material has been reviewed by Letterman Army Institute of Research and there is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the author(s) and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense. *(AR 360-5)*

Donald G. Corby 30 Oct 89

Donald G. Corby (date)
COL, MC
Commanding

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION UNCLASSIFIED	1b RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3 DISTRIBUTION / AVAILABILITY OF REPORT APPROVED FOR PUBLIC RELEASE; DISTRIBUTION IS UNLIMITED.
2b. DECLASSIFICATION / DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S) Institute Report No.: 406	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION Mammalian Toxicology Division of Toxicology 6b. OFFICE SYMBOL (If applicable) SGRD-ULE-T	7a. NAME OF MONITORING ORGANIZATION US Army Biomedical Research and Development Laboratory
6c. ADDRESS (City, State, and ZIP Code) Letterman Army Institute of Research Presidio of San Francisco, CA 94129-6800	7b. ADDRESS (City, State, and ZIP Code) Fort Detrick Frederick, MD 21701-5010
8a. NAME OF FUNDING / SPONSORING ORGANIZATION US Army Medical Research & Development Command 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
8c. ADDRESS (City, State, and ZIP Code) Fort Detrick Frederick, Maryland 21701-5012	10. SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO. 62720 / PROJECT NO. A835 / TASK NO. AB / WORK UNIT ACCESSION NO. DA303913
11. TITLE (Include Security Classification) (U) Primary Dermal Irritation Potential of DIGL-RP Solid Propellant in Rabbits	
12. PERSONAL AUTHOR(S) T.D Brown and DW Korte, Jr.	
13a. TYPE OF REPORT Institute 13b. TIME COVERED FROM 10OCT85 TO 12NOV85	14. DATE OF REPORT (Year, Month, Day) October 1989 15. PAGE COUNT 16
16. SUPPLEMENTARY NOTATION Toxicology Series No. 160	
17. COSATI CODES FIELD / GROUP / SUB-GROUP	18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number) DIGL-RP Solid Propellant, Diethyleneglycol Dinitrate, Nitrocellulose, Mammalian Toxicology, Munition, Primary Dermal Irritation, Rabbit

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

The primary dermal irritation potential of DIGL-RP Solid Propellant was determined in female New Zealand White rabbits by using a modified Draize method. DIGL-RP was applied to two sites on the back of the rabbits for a 4-hour period. No skin reaction attributable to the test compound was detected at any time during the 14-day observation period. DIGL-RP Solid Propellant was a non-irritant under conditions of this study.

20. DISTRIBUTION / AVAILABILITY OF ABSTRACT ☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT ☐ DTIC USERS	21. ABSTRACT SECURITY CLASSIFICATION UNCLASSIFIED
22a. NAME OF RESPONSIBLE INDIVIDUAL DONALD G. CORBY, COL, MC	22b TELEPHONE (Include Area Code) (415) 561-3600 22c. OFFICE SYMBOL SGRD-ULZ

DD Form 1473, JUN 86 *Previous editions are obsolete.*

ABSTRACT

The primary dermal irritation potential of DIGL-RP Solid Propellant was determined in female New Zealand White rabbits by using a modified Draize method. DIGL-RP was applied to two sites on the back of the rabbits for a 4-hour period. No skin reaction attributable to the test compound was detected at any time during the 14-day observation period. DIGL-RP Solid Propellant was a non-irritant under conditions of this study.

KEY WORDS: Primary Dermal Irritation, DIGL-RP Solid Propellant, Mammalian Toxicology, Munition, Diethyleneglycol Dinitrate, Rabbit

PREFACE

TYPE REPORT: Primary Dermal Irritation GLP Study Report

TESTING FACILITY:

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SPONSOR:

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PROJECT/WORK UNIT/APC: 3E162720A835/180/TLB0

GLP STUDY NUMBER: 85025

STUDY DIRECTOR: LTC Don W. Korte, Jr., PhD, MSC
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PRINCIPAL INVESTIGATOR: LTC Larry D. Brown, DVM, VC
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PATHOLOGIST: MAJ George T. Makovec, DVM, VC, Diplomate
American College of Veterinary Pathologists

REPORT AND DATA MANAGEMENT:

A copy of the final report, study protocol, retired SOPs, raw data, analytical, stability, and purity data of the test compound, and an aliquot of the test compound will be retained in the LAIR Archives.

TEST SUBSTANCE: DIGL-RP Solid Propellant

INCLUSIVE STUDY DATES: 10 Oct 1985 - 12 Nov 1985.

OBJECTIVE: The objective of this study was to determine the primary dermal irritation potential of DIGL-RP Solid Propellant in New Zealand White rabbits.

ACKNOWLEDGMENTS

MAJ Earl W. Morgan, DVM, SSG James D. Justus, BS, SP4 James J. Fisher, SP4 Scott L. Schwebe, SP4 Theresa L. Polk, and Yvonne C. Johnson, BS, assisted in the research. Richard A. Spieler, Diane G. Arevalo, and Obie Goodrich provided care for the animals. Colleen S. Kamiyama, Dorothy Davis, and Dianna Johnson provided secretarial assistance. Eleanor M. Baker proofread the manuscript.

SIGNATURES OF PRINCIPAL SCIENTISTS INVOLVED IN THE STUDY

We, the undersigned, declare that GLP Study 85025 was performed under our supervision, according to the procedures described herein, and that this report is an accurate record of the results obtained.

Don W. Korte, Jr 3 OCT 89

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Study Director

Larry D. Brown 13 July 1989

LARRY D. BROWN, DVM / DATE
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23 October 1989

MEMORANDUM FOR RECORD

SUBJECT: GLP Compliance for GLP Study 85Ø25

1. This is to certify that the protocol for LAIR GLP Study 85Ø25 was reviewed on 16 May 1985.

2. The institute report entitled "Primary Dermal Irritation Potential of DIGL-RP Solid Propellant," Toxicology Series 16Ø, was audited on 1Ø August 1987.

Carolyn M Lewis

CAROLYN M. LEWIS
Diplomate, American Board of
Toxicology
Quality Assurance Auditor

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Primary Dermal Irritation Potential of DIGL-RP Solid Propellant in Rabbits-
Brown and Korte

INTRODUCTION

The Department of Defense is considering the use of diethyleneglycol dinitrate (DEGDN), triethyleneglycol dinitrate (TEGDN), or trimethylolethane trinitrate (TMETN) as a replacement for nitroglycerin in new propellant formulations. However, considerable gaps in the toxicology data of the compounds were identified during a review of their health effects (1) conducted for the US Army Biomedical Research and Development Laboratory (USABRDL). Consequently, USABRDL has tasked the Division of Toxicology, Letterman Army Institute of Research (LAIR), to conduct an initial health effects evaluation of the proposed replacement nitrate esters. This initial evaluation of DEGDN, TMETN, TEGDN, and two DEGDN-based propellants, JA-2 and DIGL-RP, includes the Ames mutagenicity assay, acute oral toxicity tests in rats and mice, acute dermal toxicity in rabbits, dermal and ocular irritation studies in rabbits, and dermal sensitization studies in guinea pigs.

Objective of Study

The objective of this study was to determine the primary dermal irritation potential of DIGL-RP Solid Propellant in New Zealand White rabbits.

MATERIALS

Test Substance

Chemical Name: DIGL-RP Solid Propellant

LAIR Code Number: TP57

Description: Solid black cylinders (stick configuration)

Lot No.: RAD83M001S169

DIGL-RP Solid Propellant was received in the stick configuration. It was ground into a fine powder for this study. Other test substance information is presented in Appendix A.

Animal Data

Eight female New Zealand White rabbits (Elkhorn Rabbitry, Watsonville, CA), identified individually with ear tattooes numbered 85F229, 85F242, and 85F244 to 85F249 inclusive, were assigned to the study. The animal weights on dosing day (29 Oct 85) ranged from 2.4 to 2.6 kg. Additional animal data appear in Appendix B.

Husbandry

The rabbits were housed individually in stainless steel, screen-bottomed, battery-type cages with automatically flushing dump tanks. The diet consisted of 150 g per day of Certified Purina Chow® Diet 5322 (Ralston Purina Company, Checkerboard Square, St. Louis, MO); water was provided by continuous drip from a central line. The animal room temperature was maintained at 61°F to 69°F with a relative humidity range of 39 to 83 percent. The photoperiod was 12 hours of light per day.

METHODS

Group Assignment/Acclimation

Study animals were acclimated for 5 days to the study room following a 14-day quarantine by the Animal Resources Group. During this period they were observed daily for signs of illness. They were treated prophylactically for ear mites with a single dose of Canex® and mineral oil instilled in the ears.

Test Procedures

This study was conducted in accordance with EPA guidelines (2) and LAIR SOP-OP-STX-34 (3).

The backs of 8 rabbits were close-clipped 24 hours before the actual dosing. The clipped area was divided into 4 quadrants designated I-IV (4, 5). Site I was a sham patch control site. Sites II and III were test compound sites. Site IV was treated with a physiological saline control patch. A dose of 0.5 g of powdered DIGL-RP was mixed with 1.0 ml isotonic saline (Viaflex®, Sodium Chloride Injection, USP; Travenol Laboratories, Inc., Deerfield, IL) to make a paste, then placed on 1-inch (2.5 cm) square gauze patches that were taped to the appropriate sites. Blenderm® (Medical Products Division of 3M, Saint Paul, MN), a semi-impervious, hypoallergenic surgical tape, was used to hold the patches in place. Vet Wrap® (Animal Care Products Division of 3M, Saint Paul, MN) was then wrapped securely around the animal. The test compound was left in contact with the skin for 4 hours. At the end of the exposure period the wrapping and patches were removed, and the areas were scored one hour later.

Observations

The grading and scoring for dermal reactions were performed according to Table 1. Scoring and grading were performed at approximately 1, 24, and 48 hours, and 7 and 14 days after removal of the patch. Observations for clinical signs were made daily from 20 Oct to 12 Nov 1985. After 14 days the animals were submitted for necropsy.

Duration of Study

Appendix C is a complete historical listing of study events.

Changes/Deviations

This study was conducted in accordance with the protocol, all applicable SOPs, and addenda with the exception of calibration failures of the hygrothermograph unit in the animal room (RS1514). On 24 Oct and again on

TABLE 1 (4)
Evaluation of Skin Reactions

Erythema and Eschar Formation		
No erythema	0	
Very slight erythema (barely perceptible)	1	
Well-defined erythema	2	
Moderate-to-severe erythema	3	
Severe erythema (beet-redness to slight eschar formation [injurious in depth])	4	
Possible total erythema score		**4**
Edema Formation		
No edema	0	
Very slight edema (barely perceptible)	1	
Slight edema (edges of area well-defined by definite raising)	2	
Moderate edema (edges raised approximately 1 mm)	3	
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4	
Possible total edema score		**4**
Possible total score for primary irritation		**8**

5 Nov 85, assigned technicians noted the calibration of this unit was off by 2°F and by 10% relative humidity. The unit was immediately reset on each occasion. These deviations did not affect the outcome of this study.

Storage of Raw Data and Final Report

A copy of the final report, study protocols, raw data, retired SOPs, and an aliquot of the test compound were retained in the LAIR Archives.

RESULTS

Animals were scored for erythema and edema at each patch site. Three animals (85F229, 85F244, 85F249) exhibited very slight erythema in 2-4 quadrants during clipping and dosing and again at one hour after the wraps were removed at the end of the 4-hour exposure period. The skin was purplish pink and typified molting rabbit skin. These lesions persisted through 24 hours in one rabbit (85F244) and 72 hours in the other two (85F229, 85F249). One rabbit (85F245) had tape burns in quadrant 1 (sham patch) which was scored as very slight erythema at the 1-hour observation. The other 4 animals (85F242, 85F246, 85F247, 85F248) showed no application site reaction (skin reaction score of 0) at any time after dosing. No other recognizable skin reaction was detected at any time during the 14-day observation period. Edema was not observed at any of the exposure sites. Total scores (erythema plus edema) for the dermal irritation potential in each rabbit were tabulated (Appendix D). Fourteen days after topical application there were no gross lesions that could be attributed to exposure to the test material (Appendix E).

DISCUSSION

The modified Draize dermal irritation test as performed for this study has proven reliable for detecting non-irritating substances and severe irritants but considerably less reliable for detecting mild and moderate irritants (5). Consequently, many systems have been used to score and categorize the dermal irritation potential of a test compound. The system used by the

Toxicity Testing Program at LAIR is an adaptation of one used at the U.S. Army Environmental Hygiene Agency (6). It develops a dermal irritation index based on the peak net mean score, which is the maximum net mean score calculated during the 72-hour observation period. The dermal irritation index places the test compound into one of four categories depending on the severity of the response: non-irritant (0.0 - 0.5); mild irritant (0.51 - 2.0); moderate irritant (2.1 - 5.0); and severe irritant (5.1 - 8.0). Very slight erythema was observed in 4 of 8 rabbits but edema was not observed in any of the rabbits. Very slight erythema was observed in the control quadrants as well as test quadrants of affected animals and was consistent with terminal stages of a molt because the erythema had resolved within 72 hours. Since the erythema was observed in both test and control quadrants in each affected animal, the peak net mean score for DIGL-RP was 0 which indicated that DIGL-RP was a non-irritant in this dermal irritation assay.

DIGL-RP is relatively insoluble in physiological solutions. In order for a compound to be irritating it must first be absorbed into the skin (7). Most of the DIGL-RP applied was still present on the skin when the patches were removed. This indicates that the compound was poorly absorbed, which could account for its non-irritant effect.

CONCLUSION

The test compound DIGL-RP solid propellant is not a dermal irritant under conditions of this assay.

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2. Environmental Protection Agency. Office of Pesticide and Toxic Substances, Office of Toxic Substances (TS-792). Primary dermal irritation. In: Health effects test guidelines. Washington, DC: Environmental Protection Agency, August 1982; EPA 560/6-82-001.

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4. Draize JH, Woodard G, Calvery HO. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. J Pharmacol Exp Ther 1944; 83:377-390.

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7. Draize JH. Dermal toxicity. In: Appraisal of the safety of chemicals in foods, drugs and cosmetics. Washington: Association of Food and Drug Officials of the United States, 1965: 46-59.

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Appendix A: CHEMICAL DATA

Chemical Name: DIGL-RP Solid Propellant

LAIR Code Number: TP57

Physical State: Solid black cylinders (stick configuration)

Preparation of test substance for dosing: The cylinders of DIGL-RP were ground under liquid nitrogen using a Spex freezer mill. After grinding, the powder was sieved through an 80-mesh screen.

Chemical analysis:

DEGDN was the only major component of DIGL which could be easily analyzed. For analysis, samples of DIGL powder were added to individual 100 ml volumetric flasks.[1] After dilution to volume with 90% ethanol, a second 1:100 dilution was performed. These solutions were analyzed by HPLC. Standards consisted of solutions of DEGDN in ethanol, ranging in concentration from 164.5 to 670.5 µg/ml. Analysis of DEGDN by HPLC was performed under the following conditions: column, Brownlee RP-18 (4.6 x 250 mm, Brownlee Labs, Inc., Santa Clara, CA); solvent system, 40% water - 60% acetonitrile); flow rate, 0.9 ml/min; wavelength monitored, 210 nm.[2] Under these conditions, DEGDN eluted with a retention time of approximately 5.4 min. The results from the analysis of standards and DIGL powder samples are presented in Tables 1 and 2.

Table 1. Analysis of Standards

Concentration of Standard (µg/ml)	Peak Area* (x 10^{-7})
164.5	0.94
191.0	1.09
275.5	1.60
299.4	1.74
362.0	2.08
399.6	2.31
444.4	2.52
539.8	3.07
585.0	3.32
670.5	3.79

*Average of 2 determinations

Equation for line by linear regression analysis:

$Y = 5.62 \times 10^4 X + 3.51 \times 10^5$, $r^2 = 0.9999$

Appendix A (cont.): CHEMICAL DATA

Table 2. Analysis of DIGL Powder

Weight of DIGL Analyzed (mg)	Dilution Factor	Peak Area (x 10^{-7})	Conc. of DEGDN in DIGL (weight %)*
111.7	100	2.45	38.5
112.6	100	2.46	38.3
100.1	100	2.21	38.7

*Calculated using the equation for the standard curve as follows:
= {[Peak Area - 3.51 x 10^5]/5.62 x 10^4} ÷ wgt DIGL (mg) x 10.

The average value for the concentration of DEGDN in DIGL was 38.5% and this agrees closely with the value of 36.70 ± 1.50 reported in the manufacturer's data sheet.

Stability:

The aqueous stability of the DEGDN component in the DIGL powder was examined.[3] The amount of DEGDN in aqueous DIGL suspensions was determined immediately after preparation of a suspension and again 24 hrs later. The study was conducted as follows. A suspension of DIGL in 1% gum tragacanth (200 mg/ml) was prepared. Three 1 ml aliquots were removed from the suspension immediately after preparation and again 24 hrs later. The 1 ml samples were transferred to individual 100 ml volumetric flasks. After diluting to volume with ethanol, the flasks were shaken well. A sample from each was analyzed by HPLC as described above. The average of the peak area values was 4.03 ± 0.12 for the 0 time samples and 4.10 ± 0.14 for the 24-hour samples. These results indicate that there was no decomposition of DEGDN in 1% gum tragacanth for a period of 24 hours.

Source: Radford Army Ammunition Plant, Radford, Virginia
(prime contractor: Hercules, Inc., Wilmington, Delaware)

Lot No.: RAD83M001S169

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1 Wheeler CW. Toxicity Testing of Propellents. Laboratory Notebook #85-12-023, p. 51-61. Letterman Army Institute of Research, Presidio of San Francisco, CA.

2 Wheeler CW. Nitrocellulose-Nitroguanidine Projects. Laboratory Notebook #84-05-010.3, p. 58. Letterman Army Institute of Research, Presidio of San Francisco, CA.

3 Wheeler CW. Toxicity Testing of Propellents. Laboratory Notebook #85-12-023, p. 24-42. Letterman Army Institute of Research, Presidio of San Francisco, CA.

Appendix A (cont.): CHEMICAL ANALYSIS

Manufacturer's Data Sheet for DIGL-RP Formulation

Ingredients	Finished Propellant Percentage
Nitrocellulose (13.05 ±0.05% Nitrogen) (6-12 seconds viscosisty)	62.5 ±2.00
Diethyleneglycol Dinitrate (DEGDN)	36.70 ±1.50
Ethyl Centralite (EC)	0.25 0.25 ±0.05
Akardit II	0.25 0.45 ±0.15
Magnesium Oxide	0.05 Max
Graphite (Chg 5)	0.05 Max
	100.00

Appendix B: ANIMAL DATA

Species: *Oryctolagus cuniculus*

Strain: New Zealand White (albino)

Source: Elkhorn Rabbitry
5265 Starr Way
Watsonville, CA 95076

Sex: Male and female

Age: Young adults

Animals in each group: 8 females

Condition of animals at start of study: Normal

Body weight range at dosing: 2.4 to 2.6 kg

Identification procedures: Ear tattoo numbers 85F229, 85F242, and 85F244 - 85F249 inclusive.

Pretest conditioning:

1. Quarantine from 10 - 24 Oct 1985
2. Animal were close-clipped and examined 24 hours before dosing.

Justification: Laboratory rabbits are a proven sensitive animal model for dermal irritation.

Appendix C: HISTORICAL LISTING OF STUDY EVENTS

Date	Event
10 Oct 85	Rabbits arrived at LAIR and were examined and caged.
10 - 24 Oct 85 Care	Animals were checked daily by Division of Animal and Services personnel.
11,18,24,29 Oct 5,12 Nov 85	Animals were weighed.
18 Oct 85	Animals were tattooed and treated with Canex® and mineral oil in their ears to prevent ear mites.
24 Oct 85	Rabbits were removed from quarantine after being certified healthy by a staff veterinarian.
24 - 28 Oct 85	Animals were checked daily.
28 Oct 85	Animals were close-clipped and areas marked.
29 Oct 85	Test substance was applied for 4 hours. Areas were scored 1 hour after exposure.
30,31 Oct - 1 Nov 85	Areas were scored at 24, 48, and 72 hours after exposure.
5, 12 Nov 85	Areas scored 7 and 14 days after exposure.
12 Nov 85	Animals were submitted for necropsy.

Appendix D: DERMAL IRRITATION DATA
(Test/Sham/Vehicle)

DIGL-RP SOLID PROPELLANT

ANIMAL NUMBER	30-60 min.	24 h	48 h	72 h	7 day	14 Day
85F229*	1/1/1	1/1/1	1/1/1	1/1/1	0/0/0	0/0/0
85F242	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0
85F244*	1/1/1	0/1/1	0/0/0	0/0/0	0/0/0	0/0/0
85F245	0/1/0	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0
85F246	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0
85F247	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0
85F248	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0
85F249*	1/1/1	1/1/1	1/1/1	1/1/1	0/0/0	0/0/0
Mean	[.38/.50/.38]	[.25/.38/.38]	[.25/.25/.25]	[.25/.25/.25]	[0/0/0]	[0/0/0]
Net Mean Score†	0	0	0	0	0	0

* Baseline readings were 1/1/1 because animal was in terminal stages of a molt.

† Test Mean - (greater of Vehicle or Sham Mean) = Net Mean Score.

The peak net mean score is 0; therefore, the Primary Skin Irritation Category is I (**non-irritant**).

Appendix E: PATHOLOGY REPORT

LAIR Gross Pathology Report
GLP Study 85025

Test: Primary Dermal Irritation.

Investigator: MAJ Larry Brown.

Species: Rabbit (NZW). Sex: Female. Number: 8.

Test Substance: DIGL-RP

History: This study was conducted IAW SOP-OP-STX-34, and involved application of the compound to shaved sites of skin for predetermined periods of time and dosages.

Gross findings:

ANIMAL ID #	LAIR ACCESION #	FINDINGS
85F242	38454	Not remarkable (NR)
85F244	38455	NR
85F245	38456	NR
85F246	38457	NR
85F247	38458	NR
85F248	38459	Otitis media, right ear
85F249	38460	NR
85F229	38461	NR

Comment: The above finding was considered unrelated to the study.

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23 December 1985

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